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Review

Diagnosis and Management of Chronic Kidney Disease in the Elderly: a Field of Ongoing Debate

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ABSTRACT: Chronic kidney disease (CKD) is rather common in elderly adults who comprise the fastest growing subset of patients with end-stage renal disease (ESRD). At present, there are no specific guidelines and recommendations regarding early identification and management of elderly with CKD and the current CKD classification system may overestimate its exact prevalence. Screening strategies based either in a more accurate formula of estimation of GFR alone, or preferably in combination with proteinuria are urgently needed in order to raise awareness and to promote early diagnosis of CKD in the elderly. The number of elderly dialysis patients is also increasing and may lead to severe socio-economic problems worldwide. Both hemodialysis and peritoneal dialysis can sustain life, but present various disadvantages. There is a trend for home based dialysis therapies but the results are based on a small number of patients. Recent reports indicate that dialysis may not provide a clear benefit over non-dialysis regarding survival and quality of life issues, especially in the presence of extensive comorbidities. Current practices around the world regarding access to dialysis in the elderly are rather controversial, reflecting each country's health policies and ethical patterns. Although advanced age should not be considered as an absolute contraindication for kidney transplantation, it is not frequently offered in elderly ESRD patients due to the shortage of renal grafts. Global judgment of all physical and mental/psychological issues and full informed consent regarding possible complications are mandatory before listing elderly ESRD patients for kidney transplantation. As scientific evidence is rather scarce, there is an urgent need for prospective studies and an individualized approach for the diagnosis and treatment of the elderly CKD patients, in order to optimize care and improve quality of life in this special population.

Key words: Chronic kidney disease, elderly, hemodialysis, peritoneal dialysis, renal transplantation

The population in developed countries ages, due to the decline of mortality and the increased numbers of 'baby boomers'. In USA, the elderly are the fastest growing subpopulation, with the number of individual aged ≥ 65 years approaching above 20% of the general population by 2030 [1]. As a result, the number of older adults with Chronic Kidney Disease (CKD) is increasing. According to the United States Renal Data System, elderly adults over 65 years comprise the most rapidly increasing subset of the end-stage renal disease (ESRD) population in US [2,3]. In Europe, incident ESRD patients aged >65 years were also increased up to 55% in 2005 [4]. Patients over 65 years undergoing dialysis have a much lower life expectancy and quality of life in comparison with persons of the same age without ERSD [5,6].

In-center hemodialysis (HD) is the most frequently used kidney replacement therapy in elderly patients over 75 years [6]. Peritoneal dialysis (PD) compared to HD may improve the quality of life of elderly patients on dialysis [7]. Assisted [8] and Intermittent PD (IPD) may be alternative options for elderly patients who are unable to undergo HD or PD at home for various reasons [9]

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whereas renal transplantation is limited in the elderly [10,11].

Palliative care does not preclude dialysis and must be incorporated in the care of elderly patients with CKD and multiple geriatric syndromes in an effort to improve their quality of life [12].

Diagnosing kidney disease in the elderly

CKD is silent and asymptomatic at earlier stages and quite often undiagnosed, but can be detected by estimated Glomerular Filtration rate (eGFR) or/and albumin-to-creatinine ratio, as a marker of kidney damage.

An important question that must be addressed is whether all elderly patients classified as having CKD based on a single reduced eGFR value and without other evidence of kidney damage, should be considered as having a disease? [13]. It is important to avoid false-positive diagnoses of CKD in elderly, because this may lead to financial, social and psychological consequences [14]. Early recognition and identification of elderly patients with CKD may prevent this growing social-economic problem, as early referral to nephrologists has been associated with arrest or reversal of CKD and decreased mortality [15-17].

The Kidney Disease Outcomes Quality Initiative (KDOQI) has described a definition and a staging system of CKD relied on eGFR. At present, eGFR is considered the best indicator of kidney function and CKD is defined by a reduction of GFR < 60 mL//min and/or evidence of kidney damage, if there is proteinuria (albuminuria > 30 mg/g of creatinine), renal hematuria, or abnormal renal imaging and renal pathology for 3 months or longer [18].

Thus, CKD has been classified in 5 stages, and the same criteria are used for the diagnosis of CKD in older and in younger patients. This classification uses an estimated value of GFR rather than the measured (mGFR). mGFR can be assessed by measuring the urinary clearance of inulin,^{125} I-iotholamate, iohexol, or other exogenous filtration markers. However, all these techniques are expensive, complicated and difficult to be performed, and their use is confined to the research setting. Thus, for all of these reasons formulas based on serum creatinine have been used for the calculation of eGFR in clinical practice (Table 1).

Table 1. Equations for eGFR calculation, based on serum creatinine (Scr)

eGFR Formula Name	Equation
MDRD [28]	eGFR= 186 x Scr $^{-1.154}$ x age $^{-0.203}$ x (1.210 if black) x (0.742 if female)
CKD-EPI [35]	eGFR= 141 x min (Scr/k,1)^{a} x max (Scr/k,1) $^{-1.209}$ x 0.993 ^{age} x (1.018 if female) x (1.159 if black)
MCQ [42]	eGFR= exp[1.911+5.249/Scr- 2.114/Scr2-0.00686 x age (years)-0.205 (if female)]

MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, MCQ: Mayo Clinic Quadratic.

Creatinine Clearance (Ccr), which is often used in clinical practice, overestimates GFR due to the secretion of creatinine by the renal tubules. Moreover, Ccr is susceptible to urine collection errors especially in elderly patients [19] and is a poor screening test for CKD as it underestimates renal failure in this subpopulation [20]. Swedko et al [20] reported that a serum creatinine level greater than 1.7 mg/dL (>150 μmol/L) had an overall sensitivity of only12.6% for the detection of CKD (GFR ≤ 50 mL/min). Physicians using only serum creatinine, fail to diagnose CKD in older patients [20,21]. Branten et al have also reported that hypoalbuminemia influences the tubular secretion of creatinine leading to errors in estimation of GFR. Thus, serum creatinine is a poor marker of GFR in disease states with heavy proteinuria as in nephrotic syndrome [22].

Cockcroft-Gault formula is an equation used to estimate the endogenous creatinine clearance as follows:

Ccr=(140-age) x weight x 0.85 (if female)/(72xScr) [23]

Ccr is expressed in milliliters per minute, age in years, body weight in kilograms and serum creatinine (Scr) in milligrams per deciliter. This equation provides an estimate of Ccr but it is not equivalent to GFR due to the effect of tubular secretion of creatinine [24].

Moreover, in the Cockcroft-Gault equation body weight is considered as a surrogate for muscle mass, so it overestimates Ccr in edematous states and in obese patients [25]. Verhave et al [26] have reported that the Cockcroft-Gault equation underestimates GFR in patients over 65 years old. In addition, Cirrilo et al [27] have found that the Cockcroft-Gault equation systematically under-estimated GFR in the elderly.

The Modification of Diet in Renal Disease (MDRD) study equation was developed using data from 1628 patients with a GFR below 60 ml/min, for the estimation of GFR adjusted for $1.73m^2$ [28]. The MDRD equation was re-expressed with a standardized serum creatinine assay [29] as follows:

$$eGFR=175 \times (\text{standardized } Scr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American}).$$

The MDRD equation does not require a body weight variable and it has been recommended by the KDOQI study group for the diagnosis and classification of CKD [18]. Nevertheless, it is important to note that the use of MDRD equation leads to errors in the classification of CKD due to variable degrees of bias, imprecision and inaccuracy [24]. Therefore it is important to investigate how gold the used gold standards actually are [30]. It is worth noting the existence of differences between various laboratories regarding the calibration of the creatinine assay that leads to differences in GFR estimation [31]. Lamb et al [32] reported a similar effect of the creatinine assay calibration on eGFR estimates in older patients. They found that the effect of the calibration of creatinine assay led the Cockroft-Gault formula to underestimate the eGFR, whereas the MDRD Study equation overestimated it [32].

However, the MDRD equation has been considered as more accurate for the elderly in comparison with the Cockroft-Gault formula [33] and for this reason it has been recommended by National Kidney Foundation [18]. The MDRD equation was evolved in 1999 and was recommended by NKF in 2002, for the diagnosis and the classification of CKD but has received a lot of criticism recently. In addition, both equations overestimate mGFR in pathological states, as in nephrotic syndrome, hypo-albuminemia and in CKD at stage 5 [34].

Recently, Levey et al [35] using data from 16 studies developed a new equation to estimate GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation was developed in an attempt to create a more accurate equation than this proposed by the MDRD Study. The equation was expressed as follow:

$$eGFR = 141 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.209} \times 0.993^{Age} \times 1.018$$

Scr is serum creatinine expressed as mg/dL, k is 0.7 for females and 0.9 for males, α is -0.329 for females and – 0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.

The prevalence estimate of CKD in US by using the CKD-EPI equation was 1.6% lower than that obtained by the MDRD equation (11.5% compared to 13.1%) [36]. Moreover, the CKD-EPI equation had lower bias, especially at eGFR $\geq$ 60 ml/ min/ $1.73m^2$ [35]. Juutilainen et al [37] from Finland have also reported that the MDRD equation augmented the trend of increasing the prevalence of CKD in the general population compared with the CKD-EPI formula. Murata et al [38] have shown that the CKD-EPI equation improves performance in the healthier populations at the expense of slightly reduced performance in more diseased populations, whereas the CKD-MDRD formula provides more reliable results regarding renal function. Earley et al [39] have recently reviewed the performance of the CKD-EPI and MDRD equations and reported that both were suboptimal for all populations and GFR ranges. The MDRD Study equation was developed in a study population with CKD and a mean GFR of 40 mL/min per 1.73 m2, whereas the CKD-EPI equation was developed in a more diverse study population, including participants with and without CKD, with a mean GFR of 68 mL/min per 1.73 m^2.

It is important to note that even by the CKD-EPI formula, the prevalence of CKD in elderly remained high. The authors reported a limited number of participants older than 70 years and they also reported incomplete data on measures of muscle mass and other conditions or medications that may influence the serum creatinine [35]. Matsushita et al [40] in a meta-analysis of data from 1.1 million adults have reported that the CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and ESRD than did the MDRD equation across a broad range of populations, lowering the prevalence of CKD in all cohorts except for the elderly. Stengel et al [41] in a prospective population-based cohort study from France reported that the CKD-EPI and the MDRD equations provided very similar prevalence and long-term risk estimates in the elderly (>65 years) and an eGFR<45 ml/min/$1.73m^2$ was associated with worse outcomes.

Rule et al [42] developed the Mayo Clinic Quadratic (MCQ) equation in an effort to create a better formula for estimating GFR especially in patients with preserved kidney function. The equation was expressed as follow:

eGFR= exp[1.911+5.249/Scr- 2.114/Scr2-0.00686 x Age (years)- 0.205(if female)]

In a recent study, Carnevale et al [43] suggested that it is possible that the MCQ equation systematically overestimated GFR in patients aged over 85 years, by including age.

Cystatin C

Cystatin C is an alternative agent for estimation of GFR. It is filtered by the glomeruli and is totally reabsorbed and degraded by tubules, so it could be used as a novel agent for GFR estimation [44]. Cystatin C concentration is less dependent upon muscle mass, weight or status disease and it is dependent on kidney function, age, sex, smoking and inflammation [45,46]. New estimating equations based on cystatin C have been studied in patients with CKD, diabetes, anorexia nervosa and cystic fibrosis [47-49] (Table 2). Moreover, Stevens et al [50] reported that an equation incorporating both cystatin C and serum creatinine provides a better estimation of GFR (Table 2):

$$eGFR = \sqrt{([66.8 \text{ x } CysC)^{-1.30}] \text{ x } [273 \text{ x } (Scr)^{-1.22} \text{ x } age^{-0.299} \text{ x } 0.738(\text{if female})])}$$

Peralta et al [51] have also examined the potential benefits of adding information from a cystatin-based measure of estimated GFR and albuminuria to the current standard of CKD-EPI eGFR estimation. This triple-marker approach for predicting all-cause death and kidney failure was found to be superior compared with eGFR alone [51]. However, this approach has several limitations and can not be adopted so easily due to its additional costs and complexity for the laboratories [52]. Nevertheless, the idea of cystatin C based equations to estimate GFR seems very promising.

Table 2. Equations for eGFR based on serum cystatin C (CysC) and creatinine (Scr) in various clinical presentations.

eGFR	Equation
For CKD and anorexia nervosa	76.7 x CysC $^{-1.19}$
For CKD and anorexia nervosa	127.7 x CysC $^{-1.17}$ x age $^{-0.13}$ x (0.91 if female) x (1.06 if black)
For CKD and anorexia nervosa	177.6 x Scr $^{-0.65}$ x CysC $^{-0.57}$ x age $^{-0.20}$ x (0.82 if female) x (1.11 if black)
For CKD and diabetes	√([66.8 x CysC) $^{-1.30}$] x [273 x (Scr) $^{-1.22}$ x age$^{-0.299}$ x 0.738(if female)])
For cystic fibrosis	100/CysC-14

Limitations of the present classification system for the elderly

There are various limitations of the present classification system because it leads to over- and misdiagnosis of CKD especially in elderly. It is well known that a decline in GFR occurs with aging, so in the case of the absence of any evidence of a complication of aging, a decline in eGFR below 60 mL/min/1.73m^2 should not be considered as CKD in the elderly [53-55].

Wetzels et al [56] reported that there is a systematic decline in eGFR and mGFR at a level of 7-10 mL/min/1.73m^2 per decade after the age of 30-40 years. In addition, this age dependent decline in eGFR is not associated with the underlying renal morphology [57]. However, findings from a longitudinal study showed that the rate of the decline in GFR with ageing was greater in individuals with hypertension than without [58]. The authors reported a decline in creatinine clearance of 0.75 ml/min/year. However, one-third of subjects enrolled the study had no decline in kidney function and a small number of subjects had even an increase in creatinine clearance [58].

In addition, a moderate decline in GFR with aging may occur as part of "normal aging" [56-58] and for many nephrologists this phenomenon reflects just normal physiology. Although, not all the elderly display a decline in GFR, aged patients with a decline in renal function have probably a genetic predisposition to biological vascular aging and/or increased exposure to cardiovascular risk factors [59]. On the other hand, Gansevoort and Jong [30] suggested that "normal physiology" indicates a kind of benefit and the loss of glomeruli among elderly is not beneficial at all. Moreover, these authors have suggested that there is no strong reason to introduce age-specific cut-off values indicating CKD [30].

Regarding the prevalence of CKD stage 3, around 5-8% of the general population can be defined having CKD stage III (overall higher among elderly), whereas individuals with an eGFR around 45 mL/min/1.73m^2 are at increased risk for all cause mortality in comparison with these with higher eGFR [60,61]. Thus, for many nephrologists it should be better to subdivide CKD stage III into two stages: one not necessary pathological being 45-60 mL/min/1.73m^2 and another separate always pathologic stage being 30-45 mL/min/1.73m^2 [30]. Given all these considerations, various revisions of the current system of defining and classifying CKD have been suggested. Some revisions include lowering the threshold of eGFR below 45 mL/min/1.73m^2 for the definition of stage III [53], introducing an additional evidence of renal damage in individuals with e GFR $\geq$ 30 mL/ min/1.73m^2 in order to consider them as having CKD [54], adding two subcategories to stage III [62], introducing age- and sex-dependent thresholds after 50 years of age [60] and setting age- and sex-specific GFR reference values [60-64].

Albuminuria and CKD

The current system for the definition and classification of CKD does not include the presence of albuminuria in stages III-V. Reduced eGFR and/or proteinuria (albuminuria > 30 mg/g of creatinine) indicates a higher risk of kidney failure, cardiovascular disease, cognitive impairment and all-cause mortality in the elderly [65-69]. Moreover, Hemmelgarn et al [70] have investigated the importance of macro-abuminuria on the patients prognosis reporting that proteinuria is a worse prognostic factor in comparison with the reduction of eGFR alone and that there is a synergy between them.

According to the NHANES study, the majority (over 90%) of patients with CKD stages I and II, had only microalbuminuria (30-300 mg per day or 17-250 mg albumin/g creatinine, if men, or 25-350 mg albumin/g creatinine, if female) as a diagnostic criterion [71]. It is well known that microalbuminuria is an independent indicator of cardiovascular disease and morbidity reflecting the systemic endothelial dysfunction [72]. However, microalbuminuria can also be present, or may be influenced by other conditions not necessary "pathological" such as obesity, fever, exercise, aging and inflammation. Recent studies, have shown that patients with microalbuminuria, have an increased risk for ESRD independent of eGFR levels [73,74].

The risk of an elderly person with CKD stage 3 to develop ESRD is around 0.2-0.4% per year and the presence of concomitant proteinuria increases this risk [74]. However, patients with CKD stage 3 without micro- or macro-albuminuria have no increased risk for cardiovascular or renal events [75]. It is important to note that this group of patients constitutes 4-6% of the general population and most of them are elderly. Normoalbuminuric patients with CKD stage 3 have a better prognosis than patients with CKD stage 1 with microalbuminuria [75]. In addition, Tonelli et al [76] in a large cohort study with > 900.000 participants in Canada has reported that heavier levels of proteinuria, regardless of baseline eGFR (low, intermediate, or high), were strongly and independently associated with worse clinical outcomes.

In conclusion, microalbuminuria should be considered as a risk factor for a systemic vascular disease including kidney disease rather than a sign of CKD [76,77]. Thus, it should be re-evaluated whether microalbuminuria alone without other evidence of kidney damage is a diagnostic criterion for CKD, because its presence leads to an overestimation of CKD especially in elderly. Additional information regarding the presence of albuminuria should be incorporated in all stages of the current classification because of its prognostic value [76-78]

Our opinion is that since a new more accurate and precise equation has not been yet evolved, elderly patients with a decreased e GFR ($\leq$ 45ml/min) and concomitant proteinuria should be labeled as having definitely CKD.

Management of CKD in the elderly

At present, there are no specific guidelines and recommendations regarding early identification, and management of elderly with CKD. The major goal of a screening program should be to identify elderly with CKD at an early stage in order to prevent cardiovascular events and/or progression to ESRD.

Moreover, primary care clinicians may fail to diagnose CKD in this subset of patients and frequently these patients are not under appropriate treatment. It is well known that early referral to nephrologists has been associated with decreased mortality, better outcome and cost saving [16,17]. Pharmaceutical and life style interventions of elderly patients with CKD may have a favorable effect on patients' outcomes.

Regarding the diagnosis of CKD in elderly, many nephrologists hesitate to perform a kidney biopsy due to the possible complications. However, in elderly there is no increased risk for complications [79]. Thus, advanced age should not be considered a contraindication for kidney biopsy if indicated.

The management of elderly patients with CKD may differ to that of younger patients and there are ongoing questions regarding this issue. One concern is that at present, there is no clear consensus regarding the optimal target of blood pressure or/and the benefit of the treatment of blood pressure on the clinical outcomes among elderly patients with CKD [80]. The prevalence of isolated systolic hypertension is higher in elderly patients. In the elderly, there is a strong relation of systolic hypertension and cardiovascular complications and more focusing is needed on its treatment [81]. It is worth noting, that there is a J-shaped relationship between blood pressure and survival of elderly patients. Thus, in elderly the optimal blood pressure should be higher than in younger patients. Intensive treatment of isolated systolic pressure may lower diastolic pressure to suboptimal levels with concomitant impaired perfusion during diastole. Moreover, elderly patients may also have orthostatic hypotension which may be aggravated by anti-hypertensive treatment.

A second special issue that needs to be clarified is the management of bone disease in elderly patients with CKD at advanced stages. Bone disease and concomitant fractures has been associated with significant morbidity and mortality in the elderly. Epidemiological studies reported an increase fractures risk among patients with advanced CKD in comparison with the general population [82]. Elderly patients with CKD have two prevalent causes for bone disease: a) the osteoporosis with bone loss due to aging and b) the renal osteodystrophy due to metabolic and endocrine alterations. Thus, a new term the CKD-mineral and bone disorder (CKD-MBD) has emerged in order to understand the underlying disease process. In patients with CKD stages 1 and 2, the CKD-MBD can be managed as in the general population, whereas there are no specific recommendations regarding the pharmacological treatment of CKD-MBD in elderly patients with more advanced CKD or undergoing dialysis [83].

Dialysis vs conservative treatment

Regarding the elderly with ESRD (eGFR < 10 ml/min), there are conflicting data about survival among patients undergoing dialysis versus those receiving nondialytic management. In the US, the 1-year survival rate of patients over 80 years of age after dialysis initiation is above 54%, whereas mortality rate is high (above 20%) during the first 3 months, probably due to underlying illness and to the significant comorbidities [84].

Older age, dementia, hypoalbuminemia, diagnosis of peripheral vascular occlusive disease, and negative response to the "surprise" question "Would I be surprised if this patient died in the next 12 months?," has been recognized [85] and validated [86] as a simple and reliable method of identifying sicker incident dialysis patients with high risk for early death.

On the other hand, regarding especially the very olds there is a dilemma whether it is proper to use an expensive treatment such as HD which charges all the national health systems, or to prefer a nondialytic management in a growing subpopulation with a limited life expectancy [8]. For many nephrologists nondialytic management or delayed dialysis initiation in association with protein restriction could be an alternative strategy [87], but the benefit of this approach is needed to be proven by further studies. Kurella Tamura et al [88] studied the trajectory of functional status before and after the initiation of dialysis among elderly nursing home residents with ESRD, reporting not only high mortality rates but also a dramatic decline of functional status, with only one of eight patients maintaining their predialysis functional level. Two-thirds of patients with CKD in the study of Davison et al [89] reported that they chose HD over supportive care because it was their physician's, or family's wish, and 61% of these dialysis patients regretted having started HD, underscoring the importance of advance care planning (ACP) and suggesting the need to evaluate processes by which these patients are informed and ultimately, consent to dialysis [90]. Nephrologists are frequently balancing on a tight rope between providing their patients and their families with rather unrealistic expectations of the benefits of dialysis or explaining clearly its associated risks and its impact on survival and quality of life [91,92].

Conservative management consists of control of fluid, electrolyte balance, correction of anemia with erythropoietin if needed, pharmaceutical treatment and dietary recommendations, in order to improve the symptoms and the quality of life. Joly et al [93] from France reported that the median survival of elderly patients on dialysis was 20 months longer than that of the patients choosing nondialytic management and Murtagh et al [94] reported that the survival rates of elderly patients on HD at 1 and 2 years were higher in comparison with those obtained by conservative treatment. However, it should also be noted that the survival benefit among elderly patients with high comorbidity and ischemic heart disease was the same, either choosing dialytic or nondialytic management [94]. Recently, Chandna et al [95] reported that in patients aged over 75 years with severe comorbidities, the survival advantage obtained by dialysis is small (median survival above 5 months longer) compared with this obtained by conservative management. Large prospective studies are urgently needed to clarify the potential benefit of these two different treatments in elderly patients with ESRD.

Regarding the cost, Scalone et al [96] reported that the economic benefit of the conservative treatment with a low protein diet in elderly patients with CKD stage 5 is about 21000 euro/patient in comparison with dialysis.

Hemmelgarn et al [97] in a retrospective Canadian cohort study reported that the rates of untreated kidney failure are significantly higher in older compared with younger individuals, questioning not only the current concept [98] that elderly patients are less likely to develop ESRD compared with younger patients and are more likely to die than to progress to dialysis even at the lowest levels of eGFR, but also implicating the impact of national health systems policies.

However, except survival, that is usually small in the elderly with ESRD, quality of life issues should not be neglected. Dialysis in the elderly has been associated with impaired quality of life and loss of independence and these issues raise major ethical concerns [99,100].

Hemodialysis vs Peritoneal Dialysis

Quality of life and survival rates are two parameters which should be carefully considered in elderly patients which are candidates for starting renal replacement therapy. Some studies reported an increased risk for mortality for elderly patients on PD compared to those patients on HD [101-103].

The success of HD in elderly depends on the good function of the vascular access. Diabetes, accelerated atherosclerosis and heart failure are very common in elderly. All these parameters may contribute to a limited rate of success of a good functioning vascular access and elderly patients had an increased risk of maturation failure of arterio-venous fistulas (AVF) [104]. In addition, AVF is not benign (innocent) especially in elderly patients with high cardiovascular co-morbidity. It is well known that the creation of an AVF may aggravate persistent congestive heart failure and/or coronary artery disease [92].

HD catheters are another option and are used with a growing frequency in patients with late referral or in those patients with AVF failure [105]. Of note, catheters have obvious complications including dysfunction, central venous stenosis and infections and their use has been associated with higher rate of hospitalizations [106].

On the other hand, PD especially in elderly patients with cardiovascular disease and dysfunction of sympathetic system offers a greater sense of well-being and fewer dialysis-related symptoms including intradialytic hypotension [107]. Under certain circumstances such as congestive heart failure with moderate CKD, the use of PD with a unique exchange with icodextrin may improve the quality of life of these patients and should be considered as an alternative approach [108,109]. It should be noted that elderly patients have no increased risk for peritonitis in comparison with younger patients, but peritonitis is more lethal [110]. Paradoxically, elderly patients have lower frequency of exit-site and tunnel infection probably due to a decreased activity [111]. In addition, Nessim et al [112] reported that catheter infection was less frequent in elderly PD patients in comparison with younger patients. More recently, Lim et al [113] using data from the Australian and New Zealand Dialysis Registry reported that elderly PD patients aged over 65 years had superior technique survival and similar peritonitis-free survival compared with the younger. However, the authors confirmed that the elderly present an increased peritonitis- related mortality risk [110, 113].

PD may contribute to persistent malnutrition of elderly patients by lose of protein and free amino acids through the PD solutions. This problem can be resolved by using amino acid PD solutions and/or increased intake of dietary protein [114].

A high proportion of elderly patients present impaired cognitive function and disability. The need of assistance by family members or nurses creates further socio-economic problems especially in the health system of countries with financial problems. Assisted PD (aPD) by nurses at home and in hospital IPD [9,115] are two alternative approaches for these patients with the disadvantage of the increased cost of treatment. In France, aPD programs based on community nurses are available for a long time. Thus, PD might be the first choice of management of elderly patients over 70 years with ESRD [116].

Regarding cost-effectiveness, PD and particularly continuous ambulatory peritoneal dialysis (CAPD) have lower cost in comparison with in center HD. A recent retrospective cohort study reported that PD patients had significantly lower total healthcare costs over a 12-month follow up period. [117]. In contrast, Grun et al [118] did not find any significant difference regarding the total costs between elderly patients (≥70 years) on PD or HD. Pre-dialysis modality education may actuate the elderly patients and their family members to choose the proper treatment.

Both HD and PD have advantages and disadvantages and the final choice should be based on patients' wishes, functional status, comorbidities, financial health system policies and family/social support [92].

Kidney Transplantation in the elderly

Kidney transplantation is not frequently offered in elderly patients with ESRD due to the scarce of organs. Thus, the advanced recipient's age has been considered as a relative contraindication for kidney transplantation. However, the survival rate of elderly patients which received a kidney transplant is favorable [103]. Additionally, kidney transplantation in the elderly increases both life expectancy and quality of life [119]. According to the Scientific Registry of Transplant Recipients, elderly recipients (> 70 years) have a lower risk of mortality in comparison with elderly patients on HD which remain in the wait-list for kidney transplantation [120]. Recently, Heldal et al [121] reported that renal transplantation offers a long-term survival benefit in patients over 70 years aged. Moreover, Rebollo et al [122] reported that transplanted elderly patients had a better quality of life compared with elderly patients on HD, but the access to kidney transplantation is limited in this particular growing population [11, 120, 123], although Schaeffner et al [124] reported that in the U.S the access of elderly to transplantation doubled in the last decade.

Donor age is the major risk factor for graft loss, whereas the recipient's age does not seem to affect graft survival [125]. Thus recipient's age alone should not be considered as criterion to exclude elderly patients from renal transplantation and the elderly are doing quite well with lower doses of immunosuppressive medications [126]. However, patient selection is not an easy job for a transplant team facing a transplant candidate aged > 70 years. A global judgment of all physical and mental/psychological issues should be undertaken before the final decision to list an elderly for renal transplantation [127].

Conclusions & Perspectives

Elderly patients with CKD are a growing social and economic problem. Early identification and appropriate treatment of CKD in this population may prevent its future expansion. However, current classifications based on various eGFR formulas in the elderly, are like a fishing trawler that captures a lot of "healthy" elderly patients without overt CKD [48]. Overdiagnosis of CKD contributes to overtreatment in the form of unnecessary referrals to nephrologists and unnecessary surgeries for dialysis vascular access among patients unlikely to progress to ESRD. The consequences of underdiagnosis may range from underuse of preventive therapies to poor preparation for eventual treatment of ESRD, including late referrals for HD vascular access placement, peritoneal dialysis, or kidney transplantation. Finding the right balance between overtreatment and undertreatment is challenging but necessary. [128,129].

The association between CKD and cardiovascular disease seen in many epidemiological studies in the elderly might not be causal but just a consequence of the shared risk factors for both conditions [130,131]. The CKD-EPI equation should probably replace the MDRD equation, but the search for better filtration markers and eGFR equations should not stop. Meanwhile, a wiser cut-off level, may be an eGFR lower than 45 mL/min/1.73m^2 measured by the CKD-EPI equation [129]. Incorporation of proteinuria will definitely increase the sensitivity of the screening for CKD [76,132].

Regarding the elderly patient with ESRD, the choice to offer dialysis or not, is not so simple and should be based on patients' wishes, life expectancy, quality of life, and socio-economic status. Current practices around the world are rather controversial, reflecting each country's health policies and ethical patterns [5]. Both HD and PD can sustain life in the elderly with ESRD, but have many disadvantages. There is a trend for home based therapies (PD or home HD) but the results are based on a small number of patients and are mainly focusing on the reduced financial cost and the better quality of life at home. Palliative care should not be neglected and should be incorporated in the care of elderly patients with advanced CKD and multiple comorbidities.

There is an urgent need for large prospective studies and an individualized approach for the diagnosis and treatment of CKD in the elderly, in order to optimize care and improve quality of life in this special population. A new sub-subspeciality, the "geriatric nephrology" is coming of age [133].

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